



The Elusive Silver Bullet: FDA Failures, Rejected New Drug Applications, and the Search for an Obesity Cure

Citation

Allison Nina Canton, The Elusive Silver Bullet: FDA Failures, Rejected New Drug Applications, and the Search for an Obesity Cure (March 2011).

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**The Elusive Silver Bullet: FDA Failures, Rejected New Drug Applications, and the Search
for an Obesity Cure**

Allison N. Canton
Class of 2012
March 2011

This paper is submitted in satisfaction of the course requirement for:
Food and Drug Law
Professor Peter Barton Hutt
Winter 2011

Abstract:

Over the past forty-five years, America has fallen victim to an obesity epidemic, affecting more than thirty percent of American adults. If the incidence of obesity continues at current rates, an estimated forty-percent of Americans will be obese by 2018. Despite its widespread prevalence, treatment is limited to lifestyle modification, surgery, and pharmacotherapy. With lifestyle modification proven to be largely ineffective, surgical options reserved only for the severely obese, and only one long-term drug on the market, there is a vacuum in obesity treatment options. Moreover, the Food and Drug Administration recently rejected three promising drugs. In this paper, I review the obesity problem facing America and describe the history of anti-obesity pharmaceuticals. After examining the three recently rejected drug applications, I bring to light FDA's new priorities and offer an alternative framework for thinking about pharmacology to guide anti-obesity drug development and review.

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I. INTRODUCTION

With FDA's rejection of Contrave's new drug application (NDA), the third anti-obesity drug rejected in the past nine months, the Internet was ablaze with predictions that the anti-obesity pharmaceutical market was effectively dead. Some incensed critics alleged that FDA didn't care enough about obese Americans to let innovative new drugs come to the market. An exploration of the history of the anti-obesity pharmaceutical market in the US, however, leads one to the opposite conclusion. FDA's hesitancy to approve a new drug is a manifestation of the agency's deep concern over patient safety. And given the history of FDA-approved anti-obesity drugs that turned out to be harmful, including Meridia, which was withdrawn from the market in October 2010, it's hard to say that their concern is not well founded. In this paper, I will provide an overview of the obesity problem today in order to illustrate why a solution is urgently needed. Then, I will describe the history of anti-obesity pharmaceuticals in the US, paying particular attention to instances where FDA ultimately turned out to be wrong about the safety and efficacy of an approved drug. Next, I will chronicle three promising anti-obesity pharmaceuticals whose new drug applications (NDAs) were rejected in rapid succession over the past nine months. Finally, I will discuss the aftermath of non-approval of these NDAs and forecast an alternative framework to guide anti-obesity drug development and review.

II. OVERVIEW OF THE OBESITY PROBLEM IN THE US

a. DEMOGRAPHICS AND PREVALENCE

According to the 2008 National Health and Nutrition Examination Survey (NHANES), seventy-four percent of Americans aged twenty and older are overweight or obese.¹ Of these,

¹ Cynthia L. Ogden and Margaret D. Carroll, Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults: United States, Trends 1976-1980 Through 2007-2008 (2010).

almost half were considered obese (body mass index [BMI]² of thirty or higher).³ These rates are alarming not only for their extreme prevalence among the American population, but also for their rapid growth over the past forty-five years. Specifically, while the percentage of overweight Americans has not significantly changed since 1976, the prevalence of obesity among adults between ages twenty and seventy-four more than doubled between 1976 and 2008.⁴ If the current obesity trend continues, some studies have estimated that 43% of the U.S. population will be obese by 2018.⁵ Public health professionals have characterized the situation to be of “epidemic” proportions.⁶

The obesity epidemic has a disparate impact on minority communities, especially among women. Non-Hispanic black women and Mexican-American women are far more likely (50% and 45%, respectively) to be obese than non-Hispanic white women (33%).⁷ Evidence also suggests disparities along class lines; 15% of children aged two to four year old from low-income households are obese.⁸ The prevalence of obesity varies across the nation. While none of the states in 2009 met the 15% obesity target set forth in *Healthy People 2010*,⁹ obesity rates

² BMI is a measure of body fat based on height and weight. An adult’s BMI is calculated by dividing her weight in kilograms by the square of her height in meters. A normal BMI is between 18.5 and 24.9. An individual is considered overweight if her BMI is between 25 and 29.9 and is clinically obese if her BMI is over 30. See Centers for Disease Control and Prevention, *Healthy Weight: Assessing Your Weight: About BMI for Adults* (2009), available at http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html.

³ Ogden, *supra* note 1.

⁴ *Id.*

⁵ United Health Foundation et al., *The Future Costs of Obesity: National and State Estimates of the Impact of Obesity on Direct Health Care Expense* 9 (2009), available at <http://www.fightchronicdisease.org/pdfs/costofobesityreport-final.pdf>.

⁶ See, e.g., Youfa Wang and May A. Beydoun, *The Obesity Epidemic in the United States—Gender, Age, Socioeconomic, Racial/Ethnic, and Geographic Characteristics: A Systematic Review and Meta-Regression Analysis*, 29 *Epidemiological Reviews* 6-28 (2007).

⁷ Ogden, *supra* note 1.

⁸ National Center for Chronic Disease Prevention and Health Promotion, *Obesity: Halting the Epidemic by Making Health Easier* (2010).

⁹ U.S. Dep’t of Health and Human Services, *Healthy People 2010: Nutrition and Overweight 19-11*, available at <http://www.healthypeople.gov/2010/Document/pdf/Volume2/19Nutrition.pdf>

across the country ranged from 19% in Colorado to 34% in Mississippi.¹⁰ At least thirty percent of people were obese in nine states, up from no states in 2000.¹¹

b. THEORIES BEHIND THE GROWING OBESITY RATES

The underlying cause of obesity is an imbalance between calories consumed and calories burned. What has changed between the 1960s and the 2000s to prompt such a precipitous increase in the prevalence of obesity in the United States? The alarming rise in obesity rates has been ascribed to a number of causes. Some point to dietary changes, such as the widespread availability of high-calorie foods inside and outside the home,¹² the influence of advertising,¹³ and larger portion sizes.¹⁴ Environmental conditions are also to blame, with individuals' physical activity significantly reduced due to technological advances and the widespread ownership of automobiles.¹⁵ The Surgeon General also names genes, metabolism, behavior, environment, and culture as also contributing to the problem.¹⁶

c. OBESITY'S TOLL: INCREASED MORBIDITY & MORTALITY AND INDIRECT COSTS

Obesity is a contributing factor in over 112,000 preventable deaths each year.¹⁷ It has been linked to other chronic diseases, such as Type 2 diabetes, cardiovascular disease, and certain types of cancer.¹⁸ Researchers have suggested that an excess production of adipose tissue hormones and the resultant decrease in other types of tissue hormones is the cause of

¹⁰ Vital Signs: State-Specific Obesity Prevalence Among Adults—United States 2009, 59 MMWR (Aug. 3, 2010).

¹¹ *Id.*

¹² U.S. Dep't of Health and Human Services, The Surgeon General's Vision for a Healthy and Fit Nation (2010)

¹³ J. Lennert Veerman, et al., By How Much Would Limiting TV Food Advertising Reduce Childhood Obesity?, 19 European Journal of Public Health 365 (2009).

¹⁴ Samara Joy Nielsen and Barry M. Popkin, Patterns and Trends in Food Portion Sizes, 1977-1998, 289 JAMA 450 (2008).

¹⁵ U.S. Dep't of Health and Human Services, *supra* note 12, at 2.

¹⁶ *Id.* at 4

¹⁷ U.S. Dep't of Health and Human Services, *supra* note 12, at 2.

¹⁸ Allison Field, et al., Impact of Overweight on the Risk of Developing Common Chronic Diseases during a 10-Year Period, 161 Archives of Internal Medicine 1581 (2001).

these health problems.¹⁹ Moderate obesity (BMI of thirty to thirty-five) reduces life expectancy by three years while severe obesity (BMI greater than or equal to forty) can reduce life expectancy by up to ten years—a reduction equal to that caused by long-term smoking.²⁰ Obesity also has heavy indirect costs in the form of increased medical expenses and decreased productivity.²¹ Obese individuals also bear these economic costs personally; obese individuals spent \$1,400 more in medical costs than non-obese individuals.²²

III. OVERVIEW OF THE CURRENT ANTI-OBESITY DRUG MARKET

The history of anti-obesity drugs in the United States can fairly be characterized by the short duration that most approved medications for long-term treatment have been allowed on the market. Anti-obesity medications have been available in the United States since at least 1933, with the introduction of dinitrophenol (DNP), a cellular metabolic poison that increased metabolic rate.²³ DNP was found to increase the risk of fatal hyperthermia,²⁴ neuropathy, and cataracts.²⁵ Pursuant to its expanded powers under the 1938 Food Drugs and Cosmetics Act, the Food and Drug Administration (FDA) pressured manufacturers to withdraw DNP from the market that same year.²⁶ Since 1938, several drugs have been removed from the market because

¹⁹ Food and Drug Administration, Transcript of Endocrinologic and Metabolic Drugs Advisory Committee, July 15, 2010, at 29 (hereinafter Qnexa Advisory Committee Transcript).

²⁰ Gary Whitlock, et al., Body-Mass Index and Cause-Specific Mortality in 900,000 Adults: Collaborative Analyses of 57 Prospective Studies, 373 *Lancet* 1083 (2009).

²¹ Justin G. Trogon, et al., Indirect Costs of Obesity: a Review of the Current Literature, 9 *Obesity Reviews* 489 (2008).

²² National Center for Chronic Disease Prevention and Health Promotion, Obesity: Halting the Epidemic by Making Health Easier (2010), *available at* http://www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2010/AAG_Obesity_2010_Web_508.pdf.

²³ M.L. Tainter ML, et al., Use of Dinitrophenol in Obesity and Related Conditions: a Progress Report, 101 *Journal of the American Medical Association* 1472 (1933).

²⁴ R.B. Leftwich, et al., Dinitrophenol Poisoning: a Diagnosis to Consider in Undiagnosed Fever, 75 *Southern Medical Journal* 182 (1982).

²⁵ John Parascandola, Dinitrophenol and Bioenergetics: an Historical Perspective, 5 *Molecular and Cellular Biochemistry* 69 (1974).

²⁶ *Id.*

of serious adverse events,²⁷ while others have been restricted due to their high potential for abuse²⁸ or serious side effects.²⁹ Moreover, some drugs have failed to gain approval altogether due to FDA's safety and efficacy concerns.³⁰ Even among the drugs that have been approved, their efficacy is typically limited to a three to six month period, with partial regain of lost weight thereafter.³¹

a. THE CURRENT MARKET

i. *Phentermine*

FDA first reviewed Phentermine in 1959.³² Since phentermine is a pre-1962 drug, no efficacy trials were required for the NDA to become effective. It was, however, determined to be effective as well as safe under the drug efficacy study implementation (DESI) program, following enactment of the Drug Amendments of 1962.

Phentermine is very popular, with over six million prescriptions written for the drug in 2009.³³ Ninety-seven percent of obesity specialists reported using the drug in their practice, in contrast to sixty-four percent of specialists for the next most popular drug (diethylpropion).³⁴

Phentermine is commonly prescribed as a short-term (less than twelve weeks) treatment for overweight individuals, in combination with a regimen of exercise and a low-calorie diet.³⁵ It typically causes a four-pound weight loss per four weeks for the first eight to twelve weeks of

²⁷ I.e., aminorex (withdrawn 1965), fenfluramine (withdrawn 1997), phenylpropanolamine (withdrawn 2000), rimonabant (never approved in the US but withdrawn in Europe in 2009). See Lisa L. Ioannides-Demos, et al., Pharmacotherapies for Obesity: Past, Current, and Future Therapies, 2011 Journal of Obesity 1 (2011).

²⁸ I.e., dexamphetamine, methamphetamine. See *Id.*

²⁹ I.e., Fenfluramine (withdrawn 1997), dexfenfluramine (withdrawn 1997), phenylpropanolamine (withdrawn 2000), sibutramine (withdrawn 2010). See *Id.*

³⁰ E.g., rimonabant, lorcaserin, Qnexa, Contrave. The review process for the latter three drugs will more fully discussed below.

³¹ Lee M. Kaplan, Pharmacologic Therapies for Obesity, 39 Gastroenterology clinics of North America 69 (2010).

³² Ioannides-Demos, *supra* note 27.

³³ Qnexa Advisory Committee Transcript, *supra* note 19, at 24.

³⁴ Ed J. Hendricks, et al., How Physician Obesity Specialists Use Drugs to Treat Obesity, 17 Obesity 1730, 1732 (2009).

³⁵ National Center for Biotechnology Information, Phentermine, <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000605>.

treatment.³⁶ Side effects can include shortness of breath, chest pain, and vomiting.³⁷ Since it is closely related to amphetamine, a habit-forming drug, most people are only prescribed a three to six week course of treatment.³⁸ Therefore, phentermine is best considered a medication to help jump-start weight loss, rather than a long-term tool to manage obesity.

ii. Diethylpropion (Tenuate)

Approved by FDA in 1959, diethylpropion is an anorectant approved for short-term obesity treatment. It acts on the central nervous system and raises blood pressure in a manner similar to amphetamines.³⁹ The drug causes rapid weight loss in the first few weeks and then its efficacy tapers off, making it appropriate only for short-term weight loss. Some patients have become psychologically dependent on the drug, with extreme fatigue and mental depression occurring upon cessation in patients who were administered high doses.⁴⁰ Because of its cardiovascular effects and the potential of developing pulmonary hypertension, diethylpropion is contraindicated in individuals with hypertension or arrhythmias.⁴¹ The cardiovascular effects are amplified with extended use of the drug; the use of anorectic agents, such as diethylpropion, for a period longer than 3 months has been associated with a twenty-three-fold risk in developing pulmonary hypertension. Moreover, it is suspected that diethylpropion, like dexfenfluramine and fenfluramine, may be associated with valvular heart disease⁴² and primary pulmonary hypertension.⁴³

³⁶ Kaplan, *supra* note 31.

³⁷ National Center for Biotechnology Information, Phentermine, <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000605>.

³⁸ *Id.*

³⁹ DailyMed, Diethylpropion hcl controlled release, <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=17529>.

⁴⁰ *Id.*

⁴¹ *Id.*

⁴² *Id.*

⁴³ M.J. Abramowicz, et al., Primary Pulmonary Hypertension After Amfepramone (Diethylpropion) with BMPR2 Mutation, 3 European Respiratory Journal 560 (2003).

As is the case with many older drugs approved by FDA, there have not been many studies done on diethylpropion and few of these have studied the drug's long-term use.⁴⁴ In one recent study of sixty-nine obese adults on a hypocaloric diet, the diethylpropion group lost 9.8% of initial body weight after six months compared to a 3.2% reduction in initial body weight among subjects taking placebo.⁴⁵ The drug's effectiveness after six months was negligible. Subjects taking diethylpropion only lost less than one kilogram in months seven through twelve of the study. However, there was no evidence of a link between the drug and primary pulmonary hypertension and valvular heart disease.⁴⁶ The authors of that study surmise that the low level of interest in conducting larger studies of the long-term use of diethylpropion is likely due to the fact that the drug is no longer under patent and is relatively inexpensive.⁴⁷ Given their promising results, further larger studies are recommended in order to explore diethylpropion's long-term efficacy, either individually or in combination with other drugs, as well as to further explore its cardiovascular safety.

iii. Orlistat (Xenical/Alli)

Orlistat was approved for prescription use in 1999, three years after Hoffman-Laroche submitted an NDA for the drug. Delay in the approval process was attributable to FDA concerns over orlistat acting as a breast cancer promoter among individuals who take the drug.⁴⁸ In May 1998, FDA issued an approvable letter (meaning that the application is "basically approvable, providing certain issues are resolved"),⁴⁹ with approval contingent on the sponsor providing follow-up data from its Phase 3b studies focusing on a possible association between orlistat and

⁴⁴ C. Cercato, et al., A Randomized Double-Blind Placebo-Controlled Study of the Long-Term Efficacy and Safety of Diethylpropion in the Treatment of Obese Subjects, 33 *International Journal of Obesity* 857 (2009).

⁴⁵ *Id.*

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ Food and Drug Administration, Minutes of General Meeting Regarding NDA 20-766, Mar. 31, 1998, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_admindocs_corres_P17.pdf.

⁴⁹ 21 CFR 314.110 (2010).

breast cancer among woman aged forty-five and older.⁵⁰ Hoffman-Laroche complied and FDA deemed the data satisfactory.⁵¹

Orlistat is unlike other obesity medications since it decreases fat absorption rather than acting directly on appetite.⁵² Its prescription use (120 mg dose under the name Xenical) was approved in 1999, and it became available in a half-dose over-the-counter form (60 mg under the name Alli) in 2007. When taken with meals, orlistat can prevent absorption of up to 30% of ingested fat.⁵³ In clinical trials, patients who took the Xenical-level dose of orlistat three times a day experienced 9% weight loss over the course of one year, compared to 6% among patients who received a placebo.⁵⁴ Orlistat is not an ideal weight-loss drug because of its limited efficacy and common unpleasant gastrointestinal side effects, such as flatulence, fecal incontinence, and oily rectal discharge.⁵⁵ To minimize these side effects, the sponsor advises consumers to adopt a low-fat, reduced-calorie diet.⁵⁶ Additionally, following FDA investigation of post-marketing reports of rare but severe liver injury, both Xenical and Alli must now carry a warning.⁵⁷

b. FDA FAILURES

⁵⁰ Letter from James Bilstad, Director, Office of Drug Evaluation II, Food and Drug Administration, to Peggy Jack, Program Director- Drug Regulatory Affairs, Hoffman-LaRoche (May 12, 1998) *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_admindocs_corres_P1.pdf

⁵¹ Memorandum from Solomon Sobel, Director, Division of Metabolic and Endocrine Drug Products, Food and Drug Administration, Memorandum to the File NDA 20-766 Xenical capsules (Orlistat) (Apr. 19, 1999) *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_admindocs_corres_P1.pdf

⁵² *See* Ioannides-Demos, *supra* note 27.

⁵³ Kaplan, *supra* note 31.

⁵⁴ *Id.*

⁵⁵ Kaplan, *supra* note 31.

⁵⁶ GlaxoSmithKline, Alli Side Effects, http://www.myalli.com/About_alli/treatment_effects.aspx.

⁵⁷ Food and Drug Administration, FDA Drug Safety Communication: Completed safety review of Xenical/Alli (orlistat) and severe liver injury (May 26, 2010) *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm>

FDA's recent reticence to approve new anti-obesity medications is perhaps best explained by the recent history of withdrawals of dangerous and controversial drugs.⁵⁸

i. Fen-Phen (1997) and Dexfenfluramine (Redux) (1997)

In the early 1980s, scientists discovered that serotonin deficiency might be a physiological cause of obesity.⁵⁹ Some individuals taking SSRI-type anti-depressants that increase the amount of serotonin in the brain have experienced weight loss as a side effect of the medication.⁶⁰

Fenfluramine, a serotonin reuptake inhibitor, was approved by FDA in 1973 as a short-term treatment for obesity.⁶¹ Fenfluramine is composed of two chemicals, dexfenfluramine, an appetite suppressant, and levofenfluramine, which induces drowsiness. Because of the undesirable side effects caused by the levofenfluramine and the limited weight loss produced, fenfluramine was not a particularly popular drug.⁶² In the 1980s, an enterprising scientist, Dr. Michael Weintraub, discovered that phentermine, an approved short-term anti-obesity treatment, counteracted the drowsiness-inducing properties of fenfluramine.⁶³ The combination suppressed patients' appetites while increasing their metabolism. Dr. Weintraub published a number of studies extolling the effectiveness of the "fen-phen" combination in producing significant

⁵⁸ FDA has also taken action to remove harmful dietary supplements promoting weight loss from the market, including Ephedra (withdrawn 2006) and phenylpropanolamine (withdrawn 2000), however for the purposes of this paper, I will solely focus on drugs.

⁵⁹ J.J. Wurtman, The Involvement of Brain Serotonin in Excessive Carbohydrate Snacking by Obese Carbohydrate Cravers, 84 *Journal of the American Dietetic Association* 1004 (1984). Notably, this is also one of the first studies that pointed to the use of d-fenfluramine as a weight loss aid.

⁶⁰ D.J. Goldstein, et al., Fluoxetine: a Randomized Clinical Trial in the Treatment of Obesity, 18 *International Journal of Obesity and Related Metabolic Disorder* 129 (1994), finding that 60 mg of Prozac per day resulted in a statistically significant greater mean weight loss than placebo during the first 28 weeks of treatment. There was no difference, however, between the fluoxetine and placebo groups at 52 weeks.

⁶¹ Food and Drug Administration Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux) (Sept. 18, 1997), *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm>.

⁶² Kate Cohen, PBS Frontline: Fen Phen Nation, *available at* <http://www.pbs.org/wgbh/pages/frontline/shows/prescription/hazard/fenphen.html>.

⁶³ Michael Weintraub, et al., A Double-Blind Clinical Trial in Weight Control: Use of Fenfluramine and Phentermine Alone and in Combination, 144 *Archives of Internal Medicine* 1143 (1984).

weight-loss. In one of his studies, patients experienced a thirty-one pound reduction in body weight in the first thirty-four weeks of treatment.⁶⁴ While the weight loss produced by fen-phen was typically less than the phentermine-only regimen, the combination nonetheless produced significant weight loss and appetite control while minimizing the adverse side effects caused by either of the drugs taken alone.⁶⁵

Weintraub aggressively marketed his study results, sending reprints to doctors' offices across the nation. By February 1995, the public became aware of his research on fen-phen due to articles published in *Allure* and *Reader's Digest*.⁶⁶

Around the same time, Servier, the French sponsor of fenfluramine, discovered a way to isolate dexfenfluramine from the drowsiness-causing levofenfluramine. It sold the U.S. rights to the drug to a biotech startup who then licensed the drug to Wyeth-Ayers, to be marketed as "Redux."⁶⁷ The NDA for Redux was submitted to FDA in 1995. After reviewing the evidence, the Endocrinologic and Metabolic Drugs Advisory Committee initially recommended non-approval of the drug in a five to three vote, citing safety concerns in light of a newly published study that linked fenfluramine derivatives to primary pulmonary hypertension.⁶⁸ A new meeting was held in November 1995 to reconsider the drug and it was approved at that meeting, contingent on long-term post-marketing studies of efficacy and cardiovascular effects.⁶⁹ Some anti-Redux critics have alleged that this meeting was suspiciously rescheduled to occur during an

⁶⁴ Michael Weintraub, et al., Long-Term Weight Control Study I (Weeks 0 to 34), 51 *Clinical Pharmacology and Therapeutics* 586 (1992). Weeks 1 through 210 were published in this journal throughout 1992.

⁶⁵ Weintraub, *supra* note 63.

⁶⁶ Cohen, *supra* note 62.

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ Minutes of Food and Drug Administration, Center for Drug Evaluation and Research, Endocrinologic and Metabolic Drugs Advisory Committee Nov. 16, 1995, at 287.

international neurosciences meeting attended by many of the members of the committee who had voted against Redux.⁷⁰

Fen-phen, the combination of phentermine and either fenfluramine or dexfenfluramine, was never submitted in a new drug application to FDA.⁷¹ Instead, the combination was prescribed “off-label” by physicians and weight loss clinics around the country both for the clinically obese and people trying to lose those last few pounds.⁷² It is estimated that six million Americans took fen-phen before fenfluramine and dexfenfluramine were eventually pulled from the market.⁷³ In 1996 alone, the total number of prescriptions in the United States for fenfluramine and phentermine exceeded 18 million.⁷⁴

There were early warning signs that fenfluramine posed significant long-term health risks. Studies from the 1970s showed that even a single dose of fenfluramine administered to rats produced long-term serotonin reduction.⁷⁵ Other early studies showed that use of appetite suppressants generally tended to produce primary pulmonary hypertension (PPH), a rare but life-threatening cardiovascular disease that leads to heart failure and death within 2.5 years of diagnosis.⁷⁶ One appetite suppressant, Aminorex, approved in Europe, caused death in 50% of individuals who developed PPH as a result of taking the drug.⁷⁷ In 1995, the International Primary Pulmonary Hypertension Study found that after three months using fenfluramine or

⁷⁰ Apryl A. Ference, Rushing to Judgment on Fen-Phen and Redux, 9 Albany Law Journal of Science and Technology 77, 84 (1998) citing Michael D. Lemonick et al., *The New Miracle Drug? There's Great Excitement About Redux, the First Diet Pill Approved by the FDA in 23 Years. But It's Hardly the Ideal Way to Lose Weight*, Time, Sept. 23, 1996, at 61, 63.

⁷¹ Food and Drug Administration Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux) (Sept. 18, 1997), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm>.

⁷² Gina Kolata, *How Fen-Phen, A Diet “Miracle,” Rose and Fell*, N.Y Times Late Edition, September 23, 1997.

⁷³ *Id.*

⁷⁴ Heidi M. Connolly, et al., Valvular Heart Disease Associated with Fenfluramine-Phentermine, 337 New England Journal of Medicine 581 (1997).

⁷⁵ Una D. McCann et al., Brain Serotonin Neurotoxicity and Primary Pulmonary Hypertension from Fenfluramine and Dexfenfluramine: A Systematic Review of the Evidence, 278 JAMA 666, 667 (1997).

⁷⁶ *Id.*

⁷⁷ Gregory D. Curfman, Diet Pills Redux, 337 New Eng. J. Med. 629 (1997).

dexfenfluramine, patients were ten times more likely to develop PPH. Subjects who took the drugs for more than three months were twenty times more likely to develop the disease.⁷⁸

Serious concerns about the safety of fen-phen and Redux began to arise in the late 1990s. In July 1997, a group of doctors from the Mayo Clinic published a study reporting the incidence of heart valve disease in twenty-four women who had taken fen-phen for an average of twelve months.⁷⁹ Eight of the women in the study had also developed PPH.⁸⁰ Following publication of the study, FDA issued a public health advisory that described the Mayo Clinic findings and published a letter in the New England Journal of Medicine describing additional cases. By that time 100 cases of heart valve disease resulting from the use of fen-phen had been reported to FDA.⁸¹

The following month, FDA required phentermine, fenfluramine, and dexfenfluramine sponsors to include a black box warning on their packaging to make consumers aware of the drugs' association with valvular disease. FDA also noted that the drugs had been approved only for short-term use and for people who were significantly obese.⁸²

During this time, FDA conducted its own studies of patients taking Redux or fen-phen. The study revealed that that about 30% of subjects developed heart valve abnormalities.⁸³ Based on these study results, FDA concluded in September 1997 that fenfluramine and dexfenfluramine must be immediately withdrawn from the market.⁸⁴ FDA explained that the PPH problem was not discovered earlier because it was thought to be a highly unusual drug reaction, and thus

⁷⁸ International Primary Pulmonary Hypertension Study Group, Appetite-Suppression Drugs and the Risk of Primary Pulmonary Hypertension, 335 New England Journal of Medicine 609 (1996).

⁷⁹ See, e.g., Connolly, *supra* note 74.

⁸⁰ *Id.*

⁸¹ Food and Drug Administration Questions and Answers about Withdrawal of Fenfluramine (Pondimin) and Dexfenfluramine (Redux) (Sept. 18, 1997),

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm180078.htm>.

⁸² *Id.*

⁸³ *Id.*

⁸⁴ *Id.*

wasn't typically screened for in human clinical testing.⁸⁵ However, the Endocrinologic and Metabolic Drugs Advisory Committee was aware of the International Primary Pulmonary Hypertension Study results when it decided to approve Redux.⁸⁶

Following the withdrawal of fenfluramine and dexfenfluramine from the market, individual and class action lawsuits were filed against the manufacturers of those drugs, which were consolidated into a multi-district litigation.⁸⁷ By 1999, the plaintiffs and defense lawyers had negotiated a settlement agreement worth nearly five billion dollars that released the manufacturers from liability on most claims (notably excepting PPH claims) and provided plaintiffs with a cash or medical services benefit.⁸⁸ Litigation over fen-phen continues, with the manufacturer expecting to pay a total of twenty billion dollars to resolve the litigation.⁸⁹

ii. Sibutramine (Meridia) (2010)

FDA approved Sibutramine, marketed under the name Meridia, in November 1997,⁹⁰ shortly after fen-phen and Redux were recalled. Sibutramine acted by preventing the reuptake of norepinephrine and serotonin. But unlike fenfluramine and dexfenfluramine, sibutramine did

⁸⁵ *Id.*

⁸⁶ Minutes of the Endocrinologic and Metabolic Advisory Committee November 16, 1995, at 29.

⁸⁷ *Nation's Fen-Phen Cases Consolidated in Philly*, NATL. L.J., Dec. 29, 1997, at B2.

⁸⁸ *See, generally*, Camille N. Tragos, Fen-Phen Litigation Against American Home Products Corporation: The Widespread Use of Fenfluramine (Ponidimin) and Dexfenfluramine (Redux) for Weight Loss, the Health Problems Associated with Those Drugs, the Resulting Litigation Against American Home Products, and the Proposed Settlement Agreement, in *Food Drug Law: An Electronic Book of Student Papers*, Peter Barton Hutt, Ed.; AHP Settlement Trust, Official Notice of Final Judicial Approval, *available at* http://www.settlementdietdrugs.com/pdfs/notice_fja.pdf.

⁸⁹ Alison Frankel, *Still Ticking: Mistaken Assumptions, Greedy Lawyers, and Suggestions of Fraud Have Made Fen-phen a Disaster of a Mass Tort*, *American Lawyer*, March 2005.

⁹⁰ Food and Drug Administration, Early Communication about an Ongoing Safety Review of Meridia (sibutramine hydrochloride) (Nov. 20, 2009), *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm191650.htm>.

not release serotonin from cells. Also unlike fen-phen, no PPH or heart valve problems were reported in clinical trials.⁹¹

Because of its apparent safety and efficacy, sibutramine quickly became one of the most popularly-prescribed weight loss medications. In clinical trials, patients treated with sibutramine experienced an average weight loss of five to eight percent, compared to two to four percent weight loss among patients receiving placebo.⁹² It appeared to be most effective during the first six to twelve months of treatment. When treatment was extended for up to two years, there was an average regain of about half the weight initially lost.⁹³

These weight loss results were accompanied by some hefty side effects. Ten to fifteen percent of patients on sibutramine experienced hypertension that had to be managed by hypertensive therapy.⁹⁴ Three percent of patients discontinued the drug because of uncontrolled hypertension⁹⁵ and attrition rates in sibutramine studies were approximately thirty to forty percent.⁹⁶

FDA was well aware of these risks. During review of the sibutramine NDA, a blood pressure expert retained by FDA found that the drug increased blood pressure, but concluded that the drug's risk-benefit balance would probably only be unfavorable in obese patients with uncontrolled hypertension, coronary artery disease, congestive heart failure, stroke, or cardiac arrhythmias.⁹⁷ In light of these data, eight of the nine members of the Endocrinologic and

⁹¹ Weight Control Information Network, New Anti-obesity drug now available, WIN Notes, Summer 1998, available at <http://www.win.niddk.nih.gov/notes/summer98/artcl8.html>.

⁹² Kaplan, *supra* note 31.

⁹³ *Id.*

⁹⁴ *Id.*

⁹⁵ *Id.*

⁹⁶ D. Rucker, et al., Long Term Pharmacotherapy for Obesity and Overweight: Updated Meta-Analysis, 335 British Medical Journal 1194 (2007).

⁹⁷ Letter from Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, Food and Drug Administration, to Drs. Sidney M. Wolfe, Elizabeth Barbehenn, and Larry D. Sasich, Public Citizen (Aug. 9, 2005) available at <http://www.fda.gov/ohrms/dockets/dockets/02p0120/02p-0120-pdn0001-vol1.pdf>.

Metabolic Drugs Advisory Committee agreed that the drug's effect on blood pressure was clinically important. In balancing this risk against the potential benefits as an effective weight loss drug, the Committee split 5-4 against recommending approval.⁹⁸ Prior to rendering a final decision on the NDA, FDA requested further analyses of the clinical trial blood pressure data. Based on these findings, FDA decided to approve the drug at low and medium doses.⁹⁹

Early FDA communication about sibutramine's safety indicated that there was an increased risk of cardiovascular events such as heart attack, stroke, and cardiovascular death.¹⁰⁰ Following two sibutramine-related deaths in Britain, the European Medicines Agency (EMA) demanded a long-term trial in patients at high risk of cardiovascular disease. Preliminary results from the SCOUT study indicated that sibutramine was associated with a higher incidence of cardiovascular events (14% vs. 12% on placebo).¹⁰¹ Based on these findings, EMA concluded that further marketing of sibutramine should be suspended,¹⁰² but FDA decided to keep the drug on the market with a stronger warning label noting that sibutramine should not be used by people who have a history of stroke or heart attacks and uncontrolled blood pressure.¹⁰³

FDA acknowledged that it was aware of potential cardiovascular risks when it approved Meridia. At that time, FDA believed that these risks were monitorable and were outweighed by

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ Food and Drug Administration, Early Communication about an Ongoing Safety Review of Meridia (sibutramine hydrochloride) (Nov. 20, 2009), *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm191650.htm>.

¹⁰¹ Food and Drug Administration, Follow-Up to the November 2009 Early Communication about an Ongoing Safety Review of Sibutramine, Marketed as Meridia (Jan. 21, 2010), *available at* <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm198206.htm>.

¹⁰² European Medicines Agency, Public Statement on Zimulti: Withdrawal of the marketing authorization in the European Union (Jan. 30, 2009), *available at* <http://www.emea.europa.eu/humandocs/PDFs/EPAR/zimulti/3956009en.pdf>.

¹⁰³ Natasha Singer and Andrew Pollack, *Heart Patients Warned Against Using Meridia, an Anti-Obesity Drug*, N.Y. Times, Jan. 22, 2010, *available at* <http://www.nytimes.com/2010/01/23/business/23diet.html>.

Meridia's weight loss benefits.¹⁰⁴ The final results of the SCOUT study indicated a 16% increase in the risk of non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest, and cardiovascular death among patients who took Meridia.¹⁰⁵ Furthermore, by the end of the five-year clinical trial, Meridia was only 2.5% more effective in weight loss than placebo.¹⁰⁶ After reviewing the new clinical trial data demonstrating a significantly increased risk of cardiovascular events associated with the drug, FDA concluded in October 2010 that the benefits of Meridia outweighed the risks, and asked the manufacturer to withdraw the drug from the market.¹⁰⁷ Thus, another drug that had initially seemed very promising was taken off the market due to the unacceptable health risks posed.

IV. AN EXAMINATION OF THREE RECENTLY-REJECTED WEIGHT LOSS

NDAS

a. THE LONG ROAD FROM DRUG DEVELOPMENT TO APPROVAL

Drug development is an expensive and lengthy process. It can take ten to fifteen years, on average, for a new drug to get from initial chemical synthesis to FDA approval and it regularly costs over a billion dollars to bring a drug to market.¹⁰⁸

A manufacturer must first obtain FDA pre-market approval indicating that the drug is safe, effective, and properly labeled. In order to prove that the drug meets these criteria, the manufacturer must conduct clinical and non-clinical animal and human testing and submit their results to FDA in the form of a New Drug Application (NDA). The NDA consists of a summary, followed by information on: chemistry, manufacturing and controls; non-clinical pharmacology

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ Food and Drug Administration, Questions and Answers: FDA Recommends against Continued Use of Meridia (sibutramine) (October 8, 2010), available at <http://www.fda.gov/Drugs/DrugSafety/ucm228747.htm>.

¹⁰⁸ Peter Barton Hutt, et al., Food and Drug Law: Cases and Materials 577 (3d ed); see also Joseph A. DiMasi, et al., The Price of Innovation: New Estimates of Drug Development Costs, 22 Journal of Health Economics 151 (2003).

and toxicology; human pharmacokinetics and bioavailability; microbiology; clinical data; statistics; and proposed labeling.¹⁰⁹ The application is often developed after extensive consultation with FDA, which can help the sponsor understand and meet the agency's expectations and preview the issues that will likely be raised during review.¹¹⁰

Once the application has been filed and is accepted by FDA, a review team evaluates the study results and procedures in order to determine if the findings are valid and that the drug is safe and effective. When reviewing weight loss drugs, FDA often chooses to convene an Advisory Committee of outsiders who critique both the sponsor's and the agency's findings. The Committee pays heightened attention to the drug's risks and efficacy and develops a non-binding recommendation of approval or non-approval.¹¹¹ FDA usually takes an Advisory Committee's advice, but it is not required to do so.¹¹²

If FDA agrees with the Advisory Committee's determination that the benefits of the drug outweigh its risks, then the drug will be approved. If FDA and the Committee believe that the risks outweigh the benefits or if FDA disagrees with the Committee's recommendation for approval, FDA will issue a Complete Response Letter indicating that the agency cannot approve the application in its present form. The letter will explain the agency's reasoning and may request additional studies or notify the sponsor of other issues requiring remediation. Upon receiving the letter, the sponsor can meet with agency officials and decide to correct the deficiencies or withdraw the application.¹¹³

b. GUIDELINES FOR APPROVAL OF A WEIGHT LOSS DRUG

¹⁰⁹ Federal Food Drug and Cosmetic Act, 21 U.S.C. 355 (a)-(b)(2010); Hutt, *supra* note 108, at 676-7.

¹¹⁰ Hutt, *supra* note 108, at 683.

¹¹¹ Food and Drug Administration, The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective, available at <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>.

¹¹² *Id.*

¹¹³ *Id.*

In 2007, the FDA Advisory Committee on Endocrinologic and Metabolic Drugs issued draft guidance on weight management drugs.¹¹⁴ The guidance presents the Advisory Committee's view on a topic and suggestions for sponsors who plan to submit a NDA for a new drug or therapeutic biologic. First, the drug must be for individuals with BMI of thirty or greater or twenty-seven or greater if the obesity is accompanied by weight-related co-morbidities.¹¹⁵ Second, studies must last longer than a year in order to demonstrate the efficacy of the drug in maintaining weight loss.¹¹⁶ Phase 1 and 2 clinical trials should include a broad range of doses in order to determine the no-effect and maximally tolerated doses and to differentiate the efficacy of all doses versus placebo. Studies should also identify the effects by dose on common weight-related co-morbidities.¹¹⁷

Phase 3 clinical trials should be randomized, double-blind, and placebo-controlled and contain lifestyle modification programs that would be practicable in the real world were the drug to gain FDA approval.¹¹⁸ A drug's efficacy will be assessed by the difference in mean percent weight loss between active-product and the placebo-treated group and by the proportion of subjects who lost at least five percent of their initial body weight in the active-product versus placebo-treated group.¹¹⁹ Studies should also examine the drug's effect on blood pressure and pulse, lipids, fasting glucose and insulin, HbA1c in Type 2 diabetics, and waist circumference.¹²⁰

A drug is considered effective if *either* the difference in mean weight loss between the active-product and placebo-treated groups is at least five percent and the difference is statistically significant *or* if the proportion of subjects who lose greater than or equal to five

¹¹⁴ Food and Drug Administration, Guidance for Industry: Developing Products for Weight Management, U.S. Department of Health and Human Services (2007).

¹¹⁵ *Id.* at 4.

¹¹⁶ *Id.* at 1.

¹¹⁷ *Id.* at 5.

¹¹⁸ *Id.*

¹¹⁹ *Id.* at 6.

¹²⁰ *Id.*

percent of baseline body weight in the active-product group is at least thirty-five percent, is approximately double the proportion in the placebo group, and the difference between groups is statistically significant. Improvements in weight-related co-morbidities are also considered.¹²¹ When the sponsor has combined products, studies should compare the efficacy and safety of the combination drug versus its individual components and placebo.¹²²

The sponsor must also show that the drug is safe, through routine safety monitoring of adverse events or by specialized safety assessments if there is a known risk. If the drug acts on the central nervous system, the sponsor must show that there is no significant potential for abuse.¹²³

c. RECENT REJECTED NEW DRUG APPLICATIONS

When it comes to anti-obesity drugs, the risk-benefit calculus is far from clear. Therefore, a “yes” or “no” vote alone is hardly indicative of a committee member’s confidence of the drug. A review of the transcripts of the Advisory Committee meeting sheds much light on the members’ thinking, exposing their skepticism of a drug’s efficacy and uncertainty about its true risk profile.

i. *Qnexa (July 2010)*

Qnexa is composed of low doses of two already-approved drugs, topiramate, an anti-seizure medication that can increase satiety and alter taste,¹²⁴ and phentermine, the short-term weight loss medication discussed above. Vivus, the sponsor, submitted the NDA to FDA in December 2009.¹²⁵

¹²¹ *Id.* at 7.

¹²² *Id.* at 9.

¹²³ *Id.* at 8.

¹²⁴ Qnexa Advisory Committee Transcript, *supra* note 19, at 24.

¹²⁵ Chuck Mikolajczak, *Vivus Climbs after Qnexa NDA Submission*, Reuters, Dec. 29, 2009, available at <http://www.reuters.com/article/2009/12/29/us-markets-stocks-beforethebell-vivus-idUSTRE5BS1N220091229>.

FDA found the drug's weight loss efficacy satisfactory.¹²⁶ In one study of 200 subjects treated for a six month period, Qnexa-treated subjects lost an average of twenty-five pounds, compared to less than five pounds on placebo and ten to thirteen pounds on mono-therapy of the medication's component pharmaceuticals.^{127,128} In Phase 3 clinical trials, subjects taking the mid-level dose of Qnexa experienced an average of 8.5% weight loss and 9.2% on the high dose formulation. Treatment with the combination drug resulted in three percent greater weight loss than the component drugs.¹²⁹ Moreover, over the course of one year, Qnexa achieved a five percent greater weight loss than placebo.¹³⁰ Thus, the guidance document's standard for weight-loss drugs was met.

FDA's reluctance to approve Qnexa stemmed from safety concerns, most notably psychiatric adverse events, cognitive adverse events, metabolic acidosis, cardiovascular safety, and the teratogenicity of topiramate.¹³¹ In reviewing Qnexa's NDA, the Advisory Committee was "serious[ly] concern[ed]" about the increased incidence of depression among patients who took Qnexa in clinical trials.¹³² Sleep disorders, anxiety, and depression were responsible for twenty-six percent of adverse event-related discontinuances among study subjects treated with Qnexa.¹³³ High dose-treated subjects were twice as likely to experience psychiatric adverse events in comparison to subjects receiving placebo.¹³⁴ As for cognitive adverse events, Qnexa-

¹²⁶ Qnexa Advisory Committee Transcript, *supra* note 19, at 21.

¹²⁷ *Id.* at 35.

¹²⁸ Press Release, Vivus, Press Release: VIVUS Announces Positive Phase 2 Clinical Trial Results With Qnexa, a Novel Therapy to Treat Obesity (May 10, 2006) at <http://ir.vivus.com/releasedetail.cfm?ReleaseID=353127>.

¹²⁹ *Id.* at 119.

¹³⁰ *Id.* at 120.

¹³¹ *Id.* at 21.

¹³² Food and Drug Administration, Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee, July 15, 2010 (hereinafter Qnexa Advisory Committee Summary Minutes).

¹³³ Qnexa Advisory Committee Transcript, *supra* note 19, at 129.

¹³⁴ *Id.* at 130.

treated subjects were four times more likely to experience these.¹³⁵ The most significant cognitive adverse events were impaired attention and delayed memory; both are well-established side effects of topiramate.¹³⁶

The committee was also concerned about the dearth of data on the risks involved with co-administration of other psycho-active medicines, metabolic acidosis, and increased heart rate.¹³⁷ Unlike the fen-phen combination, however, Qnexa did not significantly increase the likelihood of serious cardiac adverse events.¹³⁸

Ironically, even the lack of effective alternative anti-obesity pharmaceuticals posed a concern to some of the committee members who voted against recommending approval:

[They] expressed an agreement that the public health consequences were too great to warrant approval, considering the risks associated with [phentermine/topiramate] and the likelihood that the heavy demand for weight loss pharmacotherapy will result in many patients exceeding dosing limitations to maximize weight loss.¹³⁹

This catch-22 pervades the regulatory environment. The committee wants drugs to be highly effective but fears the potential consequences when a highly-effective widely-used drug becomes popular. Since study subjects who discontinued using Qnexa gained back almost all of the weight lost, the drug was basically a life-long obesity treatment. Advisory Committee members were unconvinced that Qnexa was safe in the long-term, especially because of its effect on heart rate.¹⁴⁰

Despite study subject testimony that Qnexa acted like “instant willpower”, ceased their cravings for food, and caused dramatic weight loss, the Advisory Committee did not recommend

¹³⁵ *Id.* at 135

¹³⁶ *Id.* at 134-8.

¹³⁷ Qnexa Advisory Committee Summary Minutes, *supra* note 133.

¹³⁸ Qnexa Advisory Committee Transcript, *supra* note 19, at 140.

¹³⁹ Qnexa Advisory Committee Summary Minutes, *supra* note 133.

¹⁴⁰ Qnexa Advisory Committee Transcript, *supra* note 19, at 282.

approval of the NDA.¹⁴¹ It was evident that the fen-phen ordeal loomed in their memories; indeed the words “fen-phen” or “fenfluramine” appear seven times in the Advisory Committee meeting transcript. This concern was heightened in light of FDA’s recent experience with Avandia, an FDA-approved diabetes medication that has been associated with an increased risk of heart attacks. Five days before the Advisory Committee met to review Qnexa, the media was ablaze with reports that Avandia’s sponsor had withheld from FDA a study showing these risks in order to gain approval.¹⁴²

In its decision to reject Qnexa, FDA sent a message to industry that it was going to begin paying increased attention to a drug’s risk- benefit profile. Efficacy alone would not suffice. One committee member positively cited FDA’s decision to withhold approval on rimonabant, a weight loss drug that was taken off the market in Europe due to its association with increased risk of suicide.¹⁴³ Another commented, “While I’m very sympathetic to the desires of those who are seeking treatment options for this disease, I’m also equally concerned about the erosion of the public’s trust every time we approve a drug and don’t get it right the first time.”¹⁴⁴ Since obese individuals tend to have high heart rates, the committee was most seriously concerned about Qnexa’s cardiovascular effects, especially the long-term effects of high pulse rates and resultant cardiovascular adverse events like congestive heart failure.¹⁴⁵

Indeed, most of the committee members explained that they had a difficult time balancing Qnexa’s proven efficacy—“superior to anything that’s on the market”¹⁴⁶ — against its serious

¹⁴¹ *Id.* at 221.

¹⁴² Jeff Feeley and Michelle Cortez, *Ex-Regulator Said to Testify GlaxoSmithKline Withheld Study*, Businessweek, July 10, 2010, *available at* <http://www.businessweek.com/news/2010-07-10/ex-regulator-said-to-testify-glaxosmithkline-withheld-study.html>.

¹⁴³ Qnexa Advisory Committee Transcript, *supra* note 19, at 288.

¹⁴⁴ *Id.* at 317.

¹⁴⁵ *Id.* at 323.

¹⁴⁶ *Id.* at 355.

potential risks.¹⁴⁷ Many of the members expressed their desire for more long-term studies to fully explore these risks¹⁴⁸ and likened approval of the drug at this point to a “public health experiment”¹⁴⁹ due to the high potential for use by inappropriate (i.e., non-obese) populations and the minimal data on subgroups, such as gender and ethnicity, in addition to its likely use over long periods of time.

In its complete response letter to Vivus, FDA asked for a clinical and safety update evaluating topiramate’s and phentermine/topiramate’s teratogenic potential, a labeling change, and a detailed plan and strategy to evaluate and mitigate the risk of teratogenicity among woman taking the drug.¹⁵⁰ FDA also requested in an End-of-Review meeting that Vivus determine the feasibility of analyzing existing healthcare databases to determine the incidence of oral cleft in the children of women treated with topiramate for migraine.¹⁵¹

FDA’s safety concerns surrounding Qnexa were ultimately borne out; eight months after rejecting the combination drug, FDA warned consumers that topiramate, one of the component drugs, had an increased risk for oral clefts in infants born to woman treated with topiramate during pregnancy.¹⁵² This news caused a ten percent drop in Vivus stock.

But Vivus has not given up on Qnexa yet. Vivus submitted a Marketing Authorization Application with the European Medicine Agency for Qnexa in December 2010.¹⁵³ The company has completed Phase 2 clinical trials on the drug’s efficacy for treatment of obstructive sleep

¹⁴⁷ *Id.* at 349

¹⁴⁸ E.g., *Id.* at 353.

¹⁴⁹ *Id.* at 354.

¹⁵⁰ Press Release, Vivus, FDA Issues Complete Response Letter to VIVUS Regarding New Drug Application for QNEXA ® (Oct. 28, 2010) at <http://ir.vivus.com/releasedetail.cfm?ReleaseID=524576>.

¹⁵¹ Press Release, Vivus, Vivus provides Regulatory Update on QNEXA NDA (Jan. 21, 2011) at <http://ir.vivus.com/releasedetail.cfm?ReleaseID=544917>.

¹⁵² Food and Drug Administration, Topamax (topiramate): Label Change – Risk For Development of Cleft Lip and/or Cleft Palate in Newborns (Mar. 4, 2011) available at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm245777.htm>.

¹⁵³ Press Release, Vivus, VIVUS Files European marketing Authorization Application for QNEXA ® in the Treatment of Obesity (Dec. 20, 2010) at <http://ir.vivus.com/releasedetail.cfm?ReleaseID=537928>.

apnea and diabetes.¹⁵⁴ Given FDA's recent warning about topiramate, it is unclear if Vivus will succeed in resurrecting Qnexa.

ii. Lorcaserin (September 2010)

Lorcaserin is a selective serotonin 2c receptor agonist that reduces body weight by mimicking the effects of serotonin, thus decreasing food intake, increasing satiety and reducing pre-meal hunger and snacking. Unlike fenfluramine and dexfenfluramine, which acted similarly but engaged all fourteen serotonin receptors, lorcaserin avoids receptors associated with an increased risk of valvulopathy.¹⁵⁵

Arena Pharmaceuticals, the drug's sponsor, submitted the NDA in December 2009 as a long-term treatment for obesity.¹⁵⁶ The Advisory Committee reviewed lorcaserin's NDA just one day after reviewing the final SCOUT data on sibutramine that revealed a fifteen percent increased risk of heart attack. It is unsurprising, then, that the Advisory Committee displayed heightened levels of caution regarding safety. One FDA official preceded his presentation on Lorcaserin's safety and efficacy by reminding the Advisory Committee of the history of unsafe weight loss drugs.¹⁵⁷

Patients in the Phase 3 clinical trials were administered the drug and placed on a strict diet and exercise regimen.¹⁵⁸ Nearly fifty-percent (47.5%) of patients taking lorcaserin experienced five percent weight loss, compared to twenty to twenty-five percent of patients in the placebo groups.¹⁵⁹ Therefore, lorcaserin met the guidance document requirement that a weight management drug produce a five percent reduction in baseline body weight among at

¹⁵⁴ See Vivus, Pipeline: Obstructive Sleep Apnea, <http://www.vivus.com/pipeline/qnexa-obstructive-sleep-apnea>; Vivus, Pipeline: Diabetes, <http://www.vivus.com/pipeline/qnexa-diabetes>.

¹⁵⁵ Food and Drug Administration, Transcript of the Endocrinologic and Metabolic Advisory Committee, Sept. 16, 2010, at 25 (hereinafter Lorcaserin Advisory Committee Transcript).

¹⁵⁶ Arena Pharmaceuticals, Briefing Documents: NDA 22-529, Aug. 13 2010.

¹⁵⁷ Lorcaserin Advisory Committee Transcript, *supra* note 156, at 132.

¹⁵⁸ *Id.* at 44.

¹⁵⁹ *Id.* at 48.

least thirty-five percent of subjects treated with the drug, and that that proportion be approximately double the proportion of subjects losing five percent of their body weight in the placebo group.¹⁶⁰ Twenty-two percent of subjects taking lorcaserin lost ten percent of their bodyweight or more.¹⁶¹ Lorcaserin also caused modest improvements in blood pressure, lipids, and fasting blood glucose.¹⁶²

Despite meeting one of the efficacy requirements, the Advisory Committee nonetheless characterized the weight loss produced as “minimal.”¹⁶³ Most patients on lorcaserin lost between twelve and seventeen pounds,¹⁶⁴ only about three percent more than that of placebo.¹⁶⁵ Moreover, lorcaserin did not appear to be significantly more effective in maintaining a five percent weight loss in patients who continued to take the drug versus those who switched to placebo; sixty-eight percent of patients who remained on lorcaserin maintained a five percent weight loss, compared to fifty percent of patients who switched from lorcaserin to placebo.¹⁶⁶

As for lorcaserin’s safety, the Advisory Committee was very concerned about the increased incidence of tumors among rats in animal studies. Multiple tumors were found in male rats exposed to seventeen times the clinical dose.¹⁶⁷ Of most concern to the committee was that the drug caused mammary tumors among both sexes even among the lowest dose tested on

¹⁶⁰ See Food and Drug Administration, Guidance for Industry: Developing Products for Weight Management, U.S. Department of Health and Human Services (2007).

¹⁶¹ Lorcaserin Advisory Committee Transcript, *supra* note 156, at 48.

¹⁶² *Id.* at 143.

¹⁶³ Food and Drug Administration, Summary Minutes of the Endocrinologic and Metabolic Advisory Committee, Sept. 16, 2010, at 5 (hereinafter Lorcaserin Advisory Committee Summary Minutes).

¹⁶⁴ Lorcaserin Advisory Committee Transcript, *supra* note 156, at 78.

¹⁶⁵ *Id.* at 141.

¹⁶⁶ *Id.* at 51.

¹⁶⁷ *Id.* at 119.

animals, which was near clinical exposure.¹⁶⁸ The number of tumors and number of deaths related to these tumors increased with dose.¹⁶⁹

The Committee was unsure of how to translate this data to humans, given the possibility that the tumors may be due to a rodent-specific mechanism that would not affect humans. In two-year clinical trials, the study investigators did not find a consistent increase in neoplasms in patients treated with lorcaserin compared to patients given placebo (2.5% and 2.3%, respectively).¹⁷⁰ Given the discrepancy in animal versus human results, the Committee felt “unsettled” about the tumor issue.¹⁷¹

With respect to other risks, lorcaserin was not associated with an increased risk of valvulopathy over a two-year period,¹⁷² but some members of the Advisory Committee took issue with the sponsor’s statistical analysis.¹⁷³ Nor was the drug associated with increased suicidal ideation.¹⁷⁴ However, more patients taking lorcaserin experienced alterations in physical sensation and abnormal dreams or nightmares.¹⁷⁵ Patients on lorcaserin experienced three times more cognitive-related adverse events than patients receiving placebo. Most of these were related to memory, attention, and confusion.¹⁷⁶

The Committee felt that the lorcaserin clinical trials may have overestimated the real benefits and underestimated the risks due to the large number of exclusion criteria. Persons with diabetes, uncontrolled hypertension, recent heart attack or stroke, recent major depression or other psychiatric disease requiring medication, or who met the FDA definition of valvulopathy

¹⁶⁸ *Id.* at 120.

¹⁶⁹ *Id.* at 121.

¹⁷⁰ *Id.* at 61.

¹⁷¹ *Id.* at 276.

¹⁷² *Id.* at 66.

¹⁷³ *See, e.g., Id.* at 88.

¹⁷⁴ *Id.* at 71.

¹⁷⁵ *Id.* at 71.

¹⁷⁶ *Id.* at 158.

were excluded.¹⁷⁷ Twenty percent of study subjects had a history of hypertension,¹⁷⁸ compared to nearly sixty-five percent of obese and overweight individuals who take weight loss medication in the real world.¹⁷⁹

The Advisory Committee voted 5-9 that the potential benefits of Lorcaserin outweighed the potential risks when used long-term. Specifically, the marginal weight loss among unrepresentative study population would likely translate into even smaller weight loss when used in the “real world.”¹⁸⁰ There was also a labeling concern, since many populations that would use the drug (e.g., diabetics, hypertensives) were not studied.¹⁸¹ Even though the company was currently conducting a study of diabetics, the study population was not sufficiently large to allow for adequate study of the drug’s efficacy and risks.¹⁸²

If approved, the Committee recommended that Arena conduct a post-marketing trial to determine the benefits of weight loss among patients afflicted with a number of associated medical conditions. Most notably, the Committee also wanted a larger trial of several thousand patients to more effectively assess the drug’s efficacy and risk to benefits profile.¹⁸³ Such a study would be very expensive; some estimate that the cost per patient of running Phase 3 clinical studies of new drugs runs over twenty-six thousand dollars.¹⁸⁴

In response to FDA’s concerns about the mammary and brain tumors in rats, Arena is developing a three-month protocol to determine whether the tumors are malignant or benign and

¹⁷⁷ *Id.* at 139.

¹⁷⁸ *Id.* at 46.

¹⁷⁹ Food and Drug Administration, Transcript of the Endocrinologic and Metabolic Advisory Committee, Dec. 7, 2010, at 197 (hereinafter *Contrave* Advisory Committee Transcript).

¹⁸⁰ *See, e.g.*, Lorcaserin Advisory Committee Transcript, *supra* note 156, at 258.

¹⁸¹ *Id.* at 261.

¹⁸² *Id.*

¹⁸³ Lorcaserin Advisory Committee Summary Minutes, *supra* note 164, at 5.

¹⁸⁴ Phase 3 Clinical Trial Costs Exceed \$26,000 per Patient, Oct. 13, 2006, *available at* <http://www.lifesciencesworld.com/news/view/11080>.

the biological causation mechanism. FDA has requested an additional one-year study, but Arena hopes to calm their concerns with the short-term study and re-file the NDA by yearend 2011.¹⁸⁵

iii. Contrave (December 2010)

Contrave, like Qnexa, is a combination of two FDA-approved drugs, naltrexone, an opioid receptor agonist often used for alcohol and opioid addiction, and bupropion, an antidepressant that inhibits the reuptake of norepinephrine-dopamine that alone can cause significant weight loss. Orexigen Therapeutics, the drug's sponsor, submitted the NDA to FDA in March 2010 for the long-term treatment of overweight and obesity. In developing its submission, Orexigen was especially sensitive in following FDA's draft guidance and periodic advice as strictly as possible.¹⁸⁶

Contrave did not meet the first criterion for efficacy – that individuals taking the drug lose five percent or more of their body weight compared to placebo. In clinical studies, subjects taking Contrave over the course of fifty-six weeks lost 6.1% of their body weight compared to 1.3% of body weight among subjects taking placebo.¹⁸⁷ It did meet the second criterion that at least thirty-five percent of study subjects lost five percent of their initial body weight or more, double the proportion in the placebo group, and the difference between the groups was statistically significant.¹⁸⁸ In studies, between forty-five and fifty-six percent of subjects taking Contrave lost five percent of their body weight or more, in contrast to between sixteen and

¹⁸⁵ Larry Smith, *Arena Pharmaceuticals: A Nail Biting Time for Lorcaserin Approval*, Seeking Alpha, March 14, 2011, available at <http://seekingalpha.com/article/258057-arena-pharmaceuticals-a-nail-biting-time-for-lorcaserin-approval>.

¹⁸⁶ According to the head of regulatory affairs at Orexigen, "The [Contrave] development program was based on the FDA weight management guidance. We were in regular communication with the Review Division throughout the process, and the final program reflects their input." See Contrave Advisory Committee Transcript, *supra* note 180, at 27; Orexigen Therapeutics, Contrave (Naltrexone SR/Bupropion SR Combination Advisory Committee Briefing Document, at 3.

¹⁸⁷ Frank L. Greenway, et al., Effect of Naltrexone plus Bupropion on Weight Loss in Overweight and Obese Adults (COR-I): a Multicentre, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial, 376 Lancet 595 (2010).

¹⁸⁸ Food and Drug Administration, Summary Minutes of the Endocrinologic and Metabolic Advisory Committee, December 7, 2010, at 5 (hereinafter Contrave Advisory Committee Summary Minutes).

nineteen percent of subjects taking placebo.¹⁸⁹ Additionally, subjects taking Contrave experienced significant improvements in weight-related quality of life, mainly attributable to increased physical function and self-esteem.¹⁹⁰ Subjects participating in Orexigen's studies were also subjected to an intense behavioral modification plan, including group therapy.¹⁹¹ A remarkable twenty percent of placebo subjects lost ten percent or more of their body weight compared to about six percent of subjects in the placebo groups in the other trials.¹⁹²

One of the Advisory Committee members expressed frustration with Contrave's limited efficacy, typical of most weight-loss drugs. A five to ten percent reduction in body weight over the course of one year is considered a beneficial effect, even though the patient is still nowhere near a normal weight. Moreover, the pace of weight loss mimics a curve, with losing most of their weight by month six, continuing to lose weight at a slower pace through month twelve, and then plateauing or beginning to regain weight after a year, just like many other weight-loss treatments.¹⁹³

Approximately half (51% to 55%) of subjects in the active-product and placebo groups completed the Phase 3 study.¹⁹⁴ The most common adverse events that led to study withdrawal were nausea, headache, vomiting, dizziness, and insomnia.¹⁹⁵

FDA was also concerned about Contrave's safety. Bupropion, one of the drug's components, inhibits norepinephrine reuptake, which can increase blood pressure and pulse. Twice as many subjects treated with Contrave had pulse increases above 100 beats per minute in

¹⁸⁹ *Id.* at 52.

¹⁹⁰ Greenway, *supra* note 189, at 603.

¹⁹¹ Contrave Advisory Committee Transcript, *supra* note 180, at 217. Indeed, one Advisory Committee member recommended that the manufacturer package and market the behavioral modification program. *See Id.* at 312.

¹⁹² *Id.* at 157.

¹⁹³ *Id.* at 215-16.

¹⁹⁴ *Id.* at 152.

¹⁹⁵ *Id.*

two consecutive visits than subjects receiving placebo.¹⁹⁶ Subjects treated with Contrave also had small but significant increases in systolic and diastolic blood pressure.¹⁹⁷ FDA officials evaluating the sponsor's clinical studies felt that there were an insufficient number of major adverse cardiac events to effectively judge Contrave's cardiovascular safety, a point of real concern.¹⁹⁸ This was due, in part, to the researchers' failure to ensure that the study population closely mirrored the patient population at large. Specifically, only twenty-four percent of Contrave subjects were hypertensive,¹⁹⁹ as opposed to about sixty-five percent of the obese and overweight population who fill prescriptions for weight-loss drugs.²⁰⁰ While weight-loss drug sponsors are not requested to include a certain percentage of hypertensives in their studies, the failure to do so impeded the Advisory Committee's ability to evaluate Contrave's cardiovascular risks, a serious concern in light of FDA's recent experience with sibutramine.²⁰¹

Moreover, the Advisory Committee felt it had inadequate information on which to evaluate the drug's risks due to the high (46%) drop-out rate.²⁰² Members wanted to explore the drug's potential association with dizziness, anxiety, seizures, increased serum creatine, and suicidal ideation.²⁰³ The committee was also anxious to see the results of the sponsor's study on potential cardiovascular effects among high-risk populations.²⁰⁴ Eight members of the committee voted that a controlled clinical study on the drug's effect on potential major cardiac events was necessary as a condition to approval, while eleven thought that such a study could

¹⁹⁶ *Id.* at 160.

¹⁹⁷ *Id.* at 171.

¹⁹⁸ *Id.* at 172.

¹⁹⁹ *Id.* at 195.

²⁰⁰ *Id.* at 197.

²⁰¹ One Advisory Committee member commented "I want to get a better handle on whether the efficacy and the safety is reliable and it faithfully reflects what the expected efficacy and safety of this compound is going to be in the real world." *See Id.* at 197.

²⁰² Contrave Advisory Committee Summary Minutes, *supra* note 189, at 5.

²⁰³ *Id.* at 5-7.

²⁰⁴ *Id.* at 7.

be conducted post-approval. Many of the committee members struggled with this vote.²⁰⁵

Despite these concerns, thirteen of the committee members voted to recommend approval of Contrave, with seven opposing the recommendation on the grounds that that given the drug's "marginal" efficacy, the data simply didn't bear out that the benefits of the drug outweighed the risks.²⁰⁶ Even the "yes" votes were contingent on further post-approval studies.

In recording his no vote, one of the Advisory Committee members made a comment that aptly summarizes FDA's apparent position on evaluating the risk-benefit of anti-obesity drugs:

There is an opportunity for us to learn from history or else we're likely to repeat it. Every time the regulatory agency withdraws a product from the market, undoubtedly, driven by its core mission to ensure public safety, there is a price to pay for it; erosion of public trust. We need to make sure that we get it right the first time.²⁰⁷

Despite these anxieties, the Advisory Committee voted 13-7 recommending the drug's approval. Therefore, it came as a shock to when FDA informed Orexigen of its decision not to approve Contrave, citing concerns about the drug's long-term cardiovascular safety. FDA requested that the company conduct a randomized double-blind placebo-controlled study "of sufficient size and duration" to demonstrate that the risk of major cardiovascular events in patients treated with the drug doesn't adversely affect its risk-benefit profile.²⁰⁸ Such a trial would be lengthy and extremely expensive.

V. THE IMPACT OF NON-APPROVAL

²⁰⁵ *Id.* at 7.

²⁰⁶ *Id.* at 8.

²⁰⁷ Contrave Advisory Committee Transcript, *supra* note 180, at 404-5.

²⁰⁸ Press Release, Orexigen Therapeutics, Inc., FDA Issues Complete Response to New Drug Application for Contrave® for the Management of Obesity (Feb. 1, 2011) at <http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1522207&highlight=>.

The day that Orexigen announced the contents of its Complete Response Letter, a Forbes.com columnist proclaimed, “the field of obesity drugs is effectively dead... The clear lesson is that weight-loss medicines simply do not have enough of a benefit to justify any risk – and that this makes getting them approved just about impossible.”²⁰⁹ The columnist went on to predict that “a lack of scientific knowledge, high regulatory hurdles, and the fact that these failures will keep drug companies from investing in new obesity research will probably mean years, if not decades, before another weight-loss drug makes it to market.”²¹⁰

And perhaps he is right. The companies that developed Contrave, lorcaserin, and Qnexa are experiencing dire consequences as a result of their failed NDAs. Arena, lorcaserin’s sponsor, slashed twenty-five percent of its staff in the wake of FDA non-approval, hoping to save an annualized 13.5 million dollars.²¹¹ Two weeks later, its CFO resigned.²¹² Similarly, Orexigen shares fell more than seventy-two percent on the news of its non-approval.²¹³ Within days, the company announced that it was laying off forty percent of its employees in an effort to reduce annualized cash expenditures by five million dollars, allowing the company to focus on other near-term activities.²¹⁴ Other biotech companies have decided to put further anti-obesity drug

²⁰⁹ Matthew Herper, *Orexigen Rejection Kills Obesity Drug Field*, Forbes, Feb. 1, 2011, <http://blogs.forbes.com/matthewherper/2011/02/01/orexigen-rejection-kills-obesity-drug-field/>.

²¹⁰ *Id.*

²¹¹ Press Release, Arena Pharmaceuticals, Inc., Arena Pharmaceuticals Announces Workforce Reduction and Provides Lorcaserin Regulatory Update (Jan. 27, 2011) *at* <http://invest.arenapharm.com/releasedetail.cfm?ReleaseID=546080>.

²¹² Press Release, Arena Pharmaceuticals, Inc., Arena Pharmaceuticals Announces Upcoming Departure of Chief Financial Officer (Feb. 10, 2011) *at* <http://invest.arenapharm.com/releasedetail.cfm?ReleaseID=549380>.

²¹³ Katherine Hobson, *And Orexigen’s Contrave Makes 3: FDA Rejects (Another) Diet Drug*, Wall Street Journal, Feb. 1, 2011, *available at* <http://blogs.wsj.com/health/2011/02/01/and-orexigens-contrave-makes-3-fda-rejects-another-diet-drug/>.

²¹⁴ Press Release, Orexigen Therapeutics Inc., Orexigen® Therapeutics Announces Corporate Realignment (Feb. 9, 2011) *at* <http://ir.orexigen.com/phoenix.zhtml?c=207034&p=irol-newsArticle&ID=1527195&highlight=>.

development on hold in light of the financial burden of Phase 3 clinical trials and the apparently hostile regulatory environment.²¹⁵

But efforts to find a pharmaceutical obesity cure have not been entirely abandoned. As of this writing, there are still a number of drugs in the pipeline, including Phase 3 trials. For example, liraglutide, an antidiabetic medication, is being tested for its efficacy in the treatment of obesity. The manufacturer, Novo Nordisk, anticipates that the Phase 3 trials will not be completed until 2013.²¹⁶ Early clinical results are promising. In one study of pre-diabetic obese individuals, subjects on liraglutide lost nearly sixteen pounds over twenty weeks compared to a six pound weight loss among subjects receiving placebo.²¹⁷ Assuming that the drug is effective, it will likely be at least four years before it is brought to market as a weight loss treatment. Other drugs in the pipeline include zonisamide plus bupropion (completed Phase 2 clinical trials),²¹⁸ pramlintide plus metreleptin (Phase 3 trials recently suspended),²¹⁹ and tesamorelin (in Phase 2 trials).²²⁰

VI. LOOKING AHEAD

Any new anti-obesity drug NDA will undoubtedly be subject to the Advisory Committee's new stringent standards for safety and efficacy. The problem is that these standards haven't yet been formally articulated. It appears that the standards are being refined

²¹⁵ E.g., tesofensine. See NeuroSearch, NeuroSearch A/S – Financial Statements and Release of Annual Report 2010, Mar. 11, 2011, <http://www.neurosearch.dk/Default.aspx?ID=48&M=News&PID=112&NewsID=16044>.

²¹⁶ Anna Ringstrom, *Novo Nordisk to Restart Liraglutide Obesity Studies*, Reuters, Jun. 22, 2010, available at <http://www.reuters.com/article/2010/06/22/novonordisk-liraglutide-idUSLDE65L0W120100622>.

²¹⁷ Arne Astrup, et al., Effects of Liraglutide in the Treatment of Obesity: a Double-Blind, Placebo-Controlled Study, 374 *Lancet* 1606 (2009).

²¹⁸ Zonasimide plus bupropion is being developed by Orexigen, the sponsor for Contrave. Given the company's corporate realignment plans, the regulatory environment, and the expense of Phase III trials, it remains to be seen if Orexigen is willing to invest further funds in a new anti-obesity drug.

²¹⁹ Press Release, Amylin Pharmaceuticals, Inc., Amylin and Takeda Voluntarily Suspend Clinical Activities in Obesity Trial (Mar. 16, 2011) at <http://investors.amylin.com/phoenix.zhtml?c=101911&p=irol-newsArticle&ID=1539763&highlight=>.

²²⁰ Theratechnologies, Growth Hormone Deficiency in Abdominal Obesity (GHDAO), <http://www.theratech.com/en/products-therapeutic-peptides/GHDAO.php>.

as FDA responds to current events. The Committee’s concern is certainly prudent and well founded. But it is unfair to sponsors that they can develop an NDA fully compliant with Industry Guidance Document requirements but still fail to meet the Committee’s and FDA’s new expectations.

In a reflective moment, a committee member acknowledged concern about the potential impact of regulatory uncertainty on drug development efforts:

[I]t worries me tremendously to consider the chilling effect that we might provide to the Industry at large and to the future development of weight loss products if we were going to change the rules in midstream here. It was clear that the company had responsible discussions with the agency at the end of Phase 2 and before beginning the Phase 3 program. They defined the criteria and they met that [sic] criteria.²²¹

A patient advocate shared this perspective, pointing out that sponsors had abandoned metabolic pipelines because of the low likelihood of gaining approval; “Our system is such that industry and only industry can bring products to patients. When investors say that they won't support their products... we as patients pay the price....”²²²

The response to FDA’s new approach has not been entirely negative. There is a value in getting it right the first time; “We need to know exactly what the benefits are long-term, exactly what the risks are long-term before a product is approved.”²²³ Setting higher standards will force pharmaceutical sponsors to develop drugs with increased efficacy.²²⁴ Some have suggested that FDA push should sponsors to demonstrate higher efficacy but among targeted populations—thus creating a market “customized” to the patient’s profile and needs.²²⁵

²²¹ *Id.* at 315-16.

²²² *Id.* at 233-34.

²²³ *Id.* 263

²²⁴ “[T]he space program built a program to send a man to the moon, and that’s what they got.... If we want more effective drugs for weight loss, we’ve got to set higher limits.” *Id.* at 294.

²²⁵ *Id.*

In reviewing the transcripts of recent review processes, it appears that the Advisory Committee is keenly concerned about safety risks, specifically cardiovascular and cognitive risks. They criticize the efficacy requirements as too lax and essentially meaningless for obese individuals. If an obese person loses five percent of his bodyweight, he is likely still obese. Committee members would also like to see the study populations be more reflective of the obese and overweight population at large by not excluding individuals with common co-occurring morbidities like hypertension and diabetes.

The Advisory Committee members view obesity as a chronic disease, one that potentially requires treatment over the course of a lifetime. Given these facts, they are not longer willing to take a “wait and see” approach to safety and are concerned with preserving FDA’s reputation.²²⁶ However, they are also aware that there is a gap in the market that will easily be filled with “quackery” if no new effective drug for long-term use is approved soon.²²⁷

Anti-obesity drugs are considered a secondary approach to weight loss. According to the Advisory Committee’s guidance,

Lifestyle modification ... is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.²²⁸

This view is controversial given the overwhelming evidence that lifestyle modification alone is an ineffective means of promoting sustained weight loss. In one study, patients who were treated with group lifestyle modification for six months regained over thirty percent of the lost weight in

²²⁶ *Id.* at 361.

²²⁷ *Id.* at 365.

²²⁸ Food and Drug Administration, Guidance for Industry: Developing Products for Weight Management, U.S. Department of Health and Human Services 6 (Feb. 2007).

the year after treatment ended. By five years out, over fifty percent of patients had gained all of the weight lost.²²⁹

But until drug companies develop an effective anti-obesity medication with limited cardiovascular and central nervous system side effects, obesity can only be treated through a combination of surgical and lifestyle modification approaches.

Severely obese people can choose to undergo bariatric surgery, usually opting for gastric bypass or gastric banding surgery. In gastric bypass surgery, the stomach is divided to create a small upper pouch that restricts the volume of food that can be eaten. It is indicated for morbidly obese people who haven't been able to lose weight through diet and exercise and are suffering from an obesity-related health condition.

Another option for otherwise healthy but severely obese individuals (BMI greater than or equal to thirty) and moderately obese individuals (BMI greater than or equal to thirty-five) with an obesity-related health problem is gastric banding surgery. Gastric banding surgery is a procedure where an inflatable silicone ring is placed around one's stomach, thereby restricting the quantity of food than a person can eat. In one study, patients experienced a fifty-two percent weight loss for up to six years after surgery.²³⁰ FDA recently approved an expansion of the procedure to individuals with a BMI of thirty or more and an obesity-related health condition.²³¹ This means that clinically obese but otherwise healthy persons are unable to qualify for most surgical treatments, leaving the majority of obese people with weight loss drugs and lifestyle modification as their only treatment options.

²²⁹ Thomas A. Wadden, et al., Efficacy of Lifestyle Modification for Long-Term Weight Control, 12 Obesity Research 151S (2004).

²³⁰ Katie Weichman, et al., The Effectiveness of Adjustable Gastric Banding: A Retrospective 5-year U.S. Follow-up Study, 25 Surgical Endoscopy 397 (2010).

²³¹ Andrew Pollack, *F.D.A. Approves Band Device for Less Obese*, N.Y. Times, Feb. 17, 2011, at B4.

In rejecting Contrave, one Advisory Committee member commented that we still have a long way to go in understanding obesity and that the fact that we don't have an effective pharmacotherapy on the market is not enough of a reason to approve an inferior product. He urged that "a very vigorous new type of research campaign ... be launched in this country to understand this illness along new and different lines, pointing carefully to genetic and early environmental interactions.... [A]ttributing the problem to our bad behavior, and looking for drugs that will sort of push us along a bit is not going to be the final answer."²³²

VII. CONCLUSION

Are we doing obese Americans a disservice because there is a diversity of patient profiles and needs but only one drug for the long-term treatment of obesity on the market? One obesity advocate chided the Advisory Committee, "To spike all of these drugs simply because there's not a perfect drug ... is a terrible miscarriage of your duties."²³³ According to another diabetes and obesity patient advocate, patients and providers are losing trust in FDA's ability to improve life for obese people due to the hostile regulatory environment.²³⁴ We must also question the Committee's premise that five percent weight loss is insignificant among obese individuals. Some bariatric physicians have reported that even a weight loss of that small magnitude could

facilitat[e] lifestyle change, whether it decreases cravings, emotional eating, obsession with food, the noise in one's head, manages hunger; it can help break a cycle that prevents weight loss, moving a person to a new mindset. This results in metabolic improvement, decreased use of a myriad of medications, increased mobility, better self-esteem, which, in turn, perpetuates more weight loss and improved quality of life. It is a critical part of the toolbox, which helps with the strong neuroendocrine redundancy that impedes weight loss.²³⁵

²³² Contrave Advisory Committee Transcript, *supra* note 180, at 423.

²³³ *Id.* at 222.

²³⁴ *Id.* at 232.

²³⁵ *Id.* at 226.

Many public members attending the Advisory Committee meeting echoed this view,²³⁶ which is widely shared by bariatric physicians.²³⁷

Rather than being so critical of the relatively homogenous study populations in some of the critical trials, FDA should limit the approval of safe and efficacious drugs to use among individuals whose profile matches that of the clinical study population. Indeed, many researchers are pointing to individualized pharmacology as the future of medicine. In individualized medicine, the patient's treatment is tailored to her genetic or molecular profile, which improves treatment efficacy and specificity and minimizes adverse events.²³⁸ If the drug meets FDA guidance for safety and efficacy, its NDA should be approved. FDA can make that approval contingent on labeling that prescribes the drug's use only in a specific population. By permitting the use of individualized pharmacotherapy for obesity rather than a one-size-fits-all approach, obese patients can get the treatments that they desperately need. At the same time, FDA will be able to continue to protect the public's health while beginning the arduous work of regaining its trust.

²³⁶ E.g., *Id.* at 242.

²³⁷ Press Release, American Society of Bariatric Physicians, Physicians Who Treat Obesity Question FDA Rejection of Contrave (Feb. 8, 2011) at http://www.asbp.org/siterun_data/news/doc9091819141297264167.html.

²³⁸ E.g., S.A. Waldman, et al., Clinical Pharmacology: a Paradigm for Individualized Medicine, 3 *Biomarkers in Medicine* 679 (2009).